REMARKS

Claims 6, 9, 10, 17, 28-34, 36, 38-42, 46-59, and 62-69 were pending in this application. Claims 9, 10, 29, 34, 46-50, 52, 54, 56, 58, 59, and 62-67 have been canceled. Claims 17, 28, 39-42, 51, 53, 55, 57, 68, and 69 are currently amended. New claims 70-79 have been added. Accordingly, claims 6, 17, 28, 30-33, 36, 38-42, 51, 53, 55, 57, and 68-79 will be pending in the application upon entry of the instant response. Support for the claim amendments and new claims is found throughout the specification an claims as originally filed. Particular support for new claims 76-79 can be found, for example, at least at paragraph [0048] of the published specification (page 7, lines 16-22 of the application as filed).

Applicants respectfully submit that no new matter has been added to the application.

WITHDRAWAL OF PREVIOUS REJECTIONS/OBJECTIONS

Applicants acknowledge and thank the Examiner for withdrawing the previous rejection of claims 10, 28, and 39-43 under 35 U.S.C. § 112, 2nd paragraph.

RESTRICTION UNDER 35 U.S.C. §§ 121 AND 372

The Examiner has withdrawn claims 41, 51, 53, 55, 57, 59, 62, 66, and 67 from consideration as being drawn to a non-elected invention. The Examiner has taken the position that the invention as claimed fails to meet the criteria for Markush practice as set forth in MPEP 1850.III.B. Specifically, the Examiner contends that the invention as claimed fails to meet the criteria for a proper Markush group because **a common structure is NOT present in the modified RSL as claimed in claim 39** since the claimed scope encompasses those RSLs with all of the amino acid residues within P6-P'6 substituted with any amino acid residues while P1 is either R or K, and **there is NOT an**

expectation from the knowledge in the art that members of the class will behave in the same way in the context of the invention.

Applicants believe that the withdrawal of these claims from consideration on the merits is improper in view of Unity of Invention practice, as defined by PCT Rule 13, for the reasons of record submitted with the previous response. However, in order to expedite the prosecution of this application, Applicants have amended claim 39 to further clarify and define that the invention 1) has a **common property or activity** (MPEP 1850.III.B(A)) and 2) that a **common structure is present**, i.e. a significant structural element is shared by all of the alternatives (MPEP 1850.III.B(B)(2)). Applicants have amended claim 39 as follows:

A recombinant inhibitor protein, or an inhibiting fragment thereof which is at least 40% of the length of the native ACT amino acid sequence, which inhibits a kallikrein, comprising **an α-1 antichymotrypsin (ACT) serpin sequence** with a modified Reactive Serpin Loop (RSL) having an amino acid substituted sequence within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein the amino acid substitution at P1 is an arginine (R) and creates a substituted P1-P'1 scissile bond wherein the recombinant inhibitor protein, or an inhibiting fragment thereof, comprises the amino acid substituted sequence within the P6-P'6 interval selected from the group consisting of

the P3-P'2 pentapeptide SSRTE (SEQ ID NO:23),
the P3-P'2 pentapeptide KTRSN (SEQ ID NO:24),
the P4-P'1 pentapeptide ISPRS (SEQ ID NO:25),
the P4-P'1 pentapeptide GVFRS (SEQ ID NO:26),
the P4-P'1 pentapeptide GTVRS (SEQ ID NO:27),
the P4-P'1 pentapeptide ETKRS (SEQ ID NO:28),
the P3-P'2 pentapeptide LGRSL (SEQ ID NO:29),
the P3-P'2 pentapeptide RGRSE (SEQ ID NO:30),
the P2-P'3 pentapeptide RRSID (SEQ ID NO:31),
the P3-P'2 pentapeptide VLRSP (SEQ ID NO:32),
the P3-P'2 pentapeptide PFRSS (SEQ ID NO:33),
the P1-P'4 pentapeptide RSGSV (SEQ ID NO:34),
the P4-P'1 pentapeptide ARARS (SEQ ID NO:35),
the P3-P'2 pentapeptide SDRTA (SEQ ID NO:36),
the P3-P'2 pentapeptide KLRTT (SEQ ID NO:37),
the P1-P'4 pentapeptide RAAMM (SEQ ID NO:38),
the P2-P'3 pentapeptide TRAPM (SEQ ID NO:39),
the P3-P'2 pentapeptide DVRAA (SEQ ID NO:40),
the P3-P'2 pentapeptide PGRAP (SEQ ID NO:41),

the P4-P'1 pentapeptide VESRA (SEQ ID NO:42),
the P2-P'3 pentapeptide ARASE (SEQ ID NO:43),
the P4-P'1 pentapeptide TLQRV (SEQ ID NO:44),
the P4-P'1 pentapeptide RLERV (SEQ ID NO:45),
the P2-P'3 pentapeptide ERVSP (SEQ ID NO:46),
the P4-P'1 pentapeptide SSPRV (SEQ ID NO:47),
the P1-P'4 pentapeptide RVGPY (SEQ ID NO:48),
the P4-P'1 pentapeptide PSARM (SEQ ID NO:49),
the P3-P'2 pentapeptide RGRMA (SEQ ID NO:50),
the P3-P'2 pentapeptide TVRMP (SEQ ID NO:51),
the P2-P'3 pentapeptide LRMPT (SEQ ID NO:52),
the P2-P'3 pentapeptide HRMSS (SEQ ID NO:53),
the P1-P'4 pentapeptide RPQEL (SEQ ID NO:54),
the P2-P'3 pentapeptide VRPLE (SEQ ID NO:55),
the P3-P'2 pentapeptide SGRLA (SEQ ID NO:56),
the P4-P'1 pentapeptide GTLRF (SEQ ID NO:57),
the P3-P'2 pentapeptide QWRNS (SEQ ID NO:58),
the P1-P'4 pentapeptide RNDKL (SEQ ID NO:59),
the P2-P'3 pentapeptide MRNRA (SEQ ID NO:60),
the P2-P'3 pentapeptide TRDSR (SEQ ID NO:61),
the P4-P'1 pentapeptide TGSRD (SEQ ID NO:62), and
the P4-P'1 pentapeptide IMSRQ (SEQ ID NO:63).

Applicants respectfully submit that amended claim 39 clearly indicates that the claimed recombinant inhibitor proteins possess a **common structure** as required by MPEP 1850.III.B(B)(2) because the claim now specifies that the serpin sequence is **α-1 antichymotrypsin (ACT)** having a modified RSL comprising a **specific pentapeptide substituted sequence** at a **specific position within the P6-P'6 interval** selected from a **specific group of SEQ ID NOs**. It is Applicants' position that the instant claimed recombinant inhibitor proteins, or fragments thereof, all share a significant structural element because they have in common the basic sequence of ACT, including a significant portion of the RSL from ACT, but for the enumerated specific pentapeptide sequence substitutions within the P6-P'6 interval. In other words, they share in common the structure (*i.e.*, amino acid sequence) of ACT but for the internal modified pentapeptide sequences enumerated in the claims.

Additionally, Applicants respectfully submit that the claimed recombinant inhibitor proteins have a common property or activity as required by MPEP

1850.III.B(A) because they all **inhibit a kallikrein**. For example, this is clearly indicated in Table V of the specification which shows that wildtype ACT **does not inhibit** hK2, but recombinant inhibitor proteins containing pentapeptide substitutions (*e.g.* LRSRA, RRSID (SEQ ID NO:31), RGRSE (SEQ ID NO:30), KLRTT (SEQ ID NO:37), MTRSN, and ERVSP(SEQ ID NO:46)) **do inhibit hK2**. The Examiner focuses on certain differences in inhibitory profiles of various exemplified inhibitory proteins of the invention. Applicants respectfully submit, however, that this is too narrow a view, overlooking the fact that the claimed molecules share the same technical feature of the invention which is the kallikrein inhibitory activity resulting from the substituted pentapeptide sequences.

Requiring Applicants to file continuing applications to prosecute each and every species of the claimed invention would indeed be unduly burdensome, as the Examiner can appreciate. Applicants respectfully submit that the claims as presently amended are directed to a proper Markush group of molecules sharing structural properties and activity and examination of same is proper in this instant application.

In view of the above described amendments to claim 39, Applicants respectfully request that the Examiner reconsider the withdrawal of claims 41, 51, 53, 55, and 57 (claims 59, 62, 66, and 67 have been canceled) from consideration (as being drawn to a non-elected invention) and respectfully request examination of these claims on the merits.

OBJECTIONS

The Examiner has objected to claims 9 and 10 on the grounds that they contain non-elected subject matter. In view of the fact that claims 9 and 10 have been canceled, Applicants respectfully submit that this objection is moot.

REJECTIONS UNDER 35 U.S.C. § 112, 2nd PARAGRAPH

The Examiner has rejected claims 17, 40, 42, 63-65, 68, and 69 under 35 U.S.C. § 112, 2nd paragraph, for being indefinite. Specifically, the Examiner has pointed out a circular dependency between claims 40 and 63. Applicants have canceled claim 63.

Applicants have amended claims 17 and 68 to delete reference to claim 40. Applicants apologize for any inconvenience this typographical error may have caused the Examiner. Applicants respectfully submit that this rejection may now be withdrawn.

The Examiner has rejected claims 50, 52, 54, 56, and 58 under 35 U.S.C. § 112, 2nd paragraph, for lack of antecedent basis. Applicants have canceled these claims, thereby rendering this rejection moot.

The Examiner has rejected claims 68 and 69 under 35 U.S.C. § 112, 2nd paragraph, on the grounds that the phrase "modified by at least one additional substrate active site sequence" is unclear. Applicants have amended claims 68 and 69 to clarify that the recombinant inhibitor ***further comprises*** at least one additional substrate active site sequence modification. Applicants believe that this amendment addresses the Examiner's concern, and respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112, 1st PARAGRAPH

The Examiner has rejected claims 6, 9, 10, 17, 28-34, 36, 38-40, 42, 46-50, 52, 54, 56, 58, 63-65, 68, and 69 under 35 U.S.C. § 112, 1st paragraph as failing to meet the written description requirement. Specifically, the Examiner has taken the position that the scope of the claims encompasses a genus of recombinant inhibitor proteins, or inhibiting fragments thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified RSL having any amino acid substitutions within the P6-P'6 interval, wherein said serpin sequence can be attached to any amino acid sequence at N– and/or C–terminal ends, and that this results in a total number of 1.40×10^{15} possible variants to be tested. Applicants respectfully traverse the rejection.

As described above, Applicants have amended claim 39 to recite, in part, that the serpin sequence is **α-1 antichymotrypsin** and that the modified RSL comprises a **specific pentapeptide substituted sequence** at a **specific position within the P6-P'6 interval** selected from a **specific group of SEQ ID NOs**. Applicants respectfully submit that the specification and claims as originally filed clearly indicate that Applicants were

in possession of the claimed invention. However, in order to further prosecution of the instant case, amended claim 39 is now directed to a finite, and relatively small, number of recombinant inhibitor proteins, or inhibiting fragments thereof, based on α-1 antichymotrypsin (ACT). The claimed recombinant inhibitor proteins differ only by an amino acid substituted sequence with the P6-P'6 interval, wherein the amino acid substituted sequence is specified as one of a discrete group of SEQ ID NO's that substitute pentapeptide sequences at specified locations within the P6-P'6 interval.

The use of α-1 antichymotrypsin as a serpin sequence in the recombinant inhibitor protein is clearly disclosed in the specification at least at paragraphs [0063] and [0065]-[0072] and Tables III-VIII, indicating Applicants contemplated the use of recombinant inhibitor proteins containing ACT. Additionally, the working Examples (paragraphs [0142]-[0180]) present data pertaining to the actual construction and use of the aforementioned recombinant inhibitor proteins, clearly indicating Applicants were in possession of same.

The use of the claimed pentapeptide sequences as amino acid substituted sequences is also disclosed in the specification at least at paragraphs [0052]-[0056], [0065]-[0069], and [0142]-[0161], as well as Tables I, III, IV, V, and VII. Additionally, the working examples clearly indicate that Applicants had actually reduced a number of the claimed pentapeptide substitutions to actual practice (see *e.g.* Table V). It is Applicants position that the disclosure clearly indicates that Applicants contemplated the use of the claimed pentapeptide sequences, and were in possession of the same at the time of filing. Applicants submit that one of skill in the art would clearly understand that Applicants were in possession of the invention based on the above cited passages from the specification as originally filed. Applicants respectfully submit that one of skill in the art would be able to read the specification as originally filed, construct and use the invention as currently claimed without undue experimentation, and have the opportunity to improve upon the inventive concept: a central purpose of the written description requirement. For all of the foregoing reasons, Applicants respectfully request that this rejection be withdrawn.

The Examiner has further rejected claims 6, 9, 10, 17, 28-34, 36, 38-40, 42, 46-50, 52, 54, 56, 58, 63-65, 68, and 69 under 35 U.S.C. § 112, 1st paragraph as failing to meet the enablement requirement. Specifically, the Examiner has taken the position that undue experimentation would be required to test the alleged $1.40x10^{15}$ possible variants. Applicants respectfully traverse the rejection.

In view of the amendment to claim 39, Applicants respectfully submit that the claimed invention is clearly enabled by the specification and claims as originally filed. As Applicants have indicated above, amended claim 39 is directed to a finite, and relatively small, number of recombinant inhibitor proteins, or inhibiting fragments thereof, based on the α-1 antichymotrypsin (ACT) protein. As noted by the Examiner on page 15 of the Office Action, the specification provides working examples describing the use of six pentapeptide sequences for use as amino acid substituted sequences within the RSL of the recombinant inhibitor protein. Given that the scope of the claimed genus has been reduced to a relatively small number of recombinant inhibitor proteins, Applicants respectfully submit that the actual reduction to practice of the claimed invention using six such pentapeptide sequences, which represent a significant fraction of the total number of claimed pentapeptide sequences, is more than sufficient to enable one of skill in the art to make and use the invention as currently claimed. Applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102(b)

The Examiner has rejected claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 46, 47, 49, 50, 52, 54, 56, 58, 68, and 69 under 35 U.S.C. § 102(b) as being anticipated by Scheter *et al.* 1993 in view of an evidentiary reference, Rubin *et al.* 1990. Applicants respectfully traverse.

As described above, Applicants have amended claim 39 to be directed to recombinant inhibitor proteins comprising a serpin sequence that is **α-1 antichymotrypsin** comprising a modified RSL having an **amino acid substituted sequence within the P6-P'6 interval, wherein** the amino acid substituted sequence is selected from a **specific group of SEQ ID NOs.** In response to Applicants arguments of record filed with the December 12, 2007 response, the Examiner has stated that

> "contrary to Applicants' allegation that the claims are not anticipated because Scheter *et al.* do not teach recombinant inhibitor proteins comprising pentapeptide within the RSL, **it is noted by the Examiner that such limitation is NOT recited in the claims rejected herein**...(emphasis added; page 19-20)"

In view of the fact that the Examiner's reasoning for maintaining the rejection is based on the allegation that a pentapeptide limitation was not incorporated into the base claim, Applicants respectfully submit that the amendment of claim 39 to incorporate such a pentapeptide limitation is sufficient to overcome this rejection for the reasons previously stated of record. Applicants respectfully request that that this rejection be withdrawn.

For at least the foregoing reasons, Applicants submit that the instant application is in condition for allowance, and such allowance is respectfully requested.

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Respectfully submitted,

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